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# ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Hepatology
**ESPS manuscript NO:** 24517
**Title:** Is neutrophil gelatinase associated lipocalin a marker of renal impairment in HCV infection? Evaluation before and after therapy containing directly acting antivirals.
**Reviewer's code:** 03473461
**Reviewer's country:** United States
**Science editor:** Jing Yu
**Date sent for review:** 2016-01-27 12:37
**Date reviewed:** 2016-02-04 02:26

| CLASSIFICATION | LANGUAGE EVALUATION | SCIENTIFIC MISCONDUCT | CONCLUSION |
|---|---|---|---|
| [ ] Grade A: Excellent | [ ] Grade A: Priority publishing | Google Search: | [ ] Accept |
| [ ] Grade B: Very good | [Y] Grade B: Minor language polishing | [ ] The same title | [ ] High priority for publication |
| [Y] Grade C: Good | [ ] Grade C: A great deal of language polishing | [ ] Duplicate publication | [ ] Rejection |
| [ ] Grade D: Fair | [ ] Grade D: Rejected | [ ] Plagiarism | [ ] Minor revision |
| [ ] Grade E: Poor | | [Y] No | [Y] Major revision |
| | | BPG Search: | |
| | | [ ] The same title | |
| | | [ ] Duplicate publication | |
| | | [ ] Plagiarism | |
| | | [Y] No | |

## COMMENTS TO AUTHORS

Summary This study examined the measures of a novel biomarker for kidney function, neutrophil gelatinase associated lipocalin before and after HCV treatment with direct acting antivirals among 48 patients. Major points 1. The motiviation for the study can be improved. It's unclear why clinicians or policy makers should be interested in NGAL as a diagnostic tool? Is NGAL less expensive than other tests? Does it predict severe outcomes more accurately? If extreme values NGAL indicate toxicity, should extreme values be interpreted as a reason to discontinue treatment? Since NGAL is traditionally a measure of kidney function, what is the current clinical or theoretical understanding of kidney function and HCV infection? If there is a relationship between eGFR and NGAL, what is the relevance of eGFR to HCV infection status, diagnosis, liver disease, or HCV-related prognoses? 2. This empirical support for the study's primary conclusion is weak. The only stated conclusion, apart from that the clinical use of NGAL is not clear, is that NGAL could provide complementary information to eGFR. But this conclusion seems contradicted by the data presented in Figure 4, which shows minimal resemblance between NGAL and eGFR. In addition, the

primary piece of evidence that seems to support this one conclusion seems to be found in panel B of Figure 2, which shows a very subtle downward slope, significant at 4.88%, between NGAL and eGFR. Unfortunately, the limited number of observations in this study does not warrant much confidence in this measurement. While statistically significant, this relationship could be due random chance or a mixture of random chance and some other small effects, such as age, that are being mediated by eGFR. Stronger evidence for this conclusion would include a much more coherent conceptual model of inflammation paired with an empirical model that estimates the relationship between NGAL and eGFR while controlling for potential confounders identified in the conceptual model such as age, gender, hcv genotype, and treatment status. Minor points (page number . approx location on page) Title. The title does not represent the content of the paper. The title should be something like "Is neutrophil gelatinase useful in assessing the health of patients with hepatitis C infection?" In particular, I don't think paper's title should make reference to "before and after therapy containing DAAs". There's just too few observations of patients under treatment to justify stating treatment as a prominent component of the study. There's only 8 observations of patients under treatment, so at most, a discussion of the associations before and after treatment should be a small part of the results. Abstract. Remove or revise the following statement from the abstract "Not statistically significant differences were demonstrated after 1 year." This statement doesn't reference any variables, so its impossible to tell what the "differences" are between or in reference to. General. The paper needs line numbers during the review process. 8. 3rd paragraph. Please justify the choice of 65 years as a threshold age. Is the justification based on the median or mean value of the age variable? If not, the justification should include some biological or conceptual reasoning for choosing 65, instead of any other arbitrary value such as 60, or 50, or 70. If the choice of 65 is arbitrary, then additional sensitivity analyses should be conducted comparing NGAL values across different age thresholds. 8.last paragraph. "…an univariate" should be "a univariate" 10. 1st paragraph. Can remove "at linear regression analysis" Figure 2. Replace Figure 2 with a table that presents the univariate model results, coefficients, standard errors, p-values, R2, and observation counts. In particular, why does it look like there are a lot fewer FIB4 observations than the others? Figure 3. As a comparison, this figure should contain two additi

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| | | [ ] Plagiarism | |
| | | [Y] No | |

## COMMENTS TO AUTHORS

Comments to the Authors: This is a small, prospective study of 48 patients with chronic hepatitis C who underwent NGAL testing. Eight patients were then started on HCV therapy and NGAL was evaluated at week 4 and week 12 of therapy. I think the clinical relevance of the study is low at this point, especially as the HCV therapy described in the manuscript was primarily PEG/RBV/TVR. However this perhaps could fuel further research on the topic as you suggest. I think the main novel findings of the study are that NGAL did not predict worsening eGFR and that NGAL increased in patients (though a very small N) on HCV therapy. The first research finding is different to what has been found before and the second research finding has not been looked at previously. I think this should be the focus of the paper -- the other analyses were almost all non-significant and do not add anything substantial to this manuscript. I highlighted other questions/concerns below. Title: - I think the title is misleading, because the majority of patients included in the study were not evaluated before/after DAA therapy. Additionally, it appears from the manuscript that NGAL levels were obtained during therapy, but not after therapy Introduction - I think a brief explanation of the

differences between plasma and urinary NGAL would be helpful, and then maybe later they should indicate why they chose plasma NGAL instead of urinary NGAL - Is there something that makes NGAL particularly useful in cirrhotic patients? Materials and Methods: Groups of Patients - Why was an HCV VL of 1,000,000 used as a cut-off? Materials and Methods: Statistical Analysis - Why only perform a univariate analysis? The factors that were felt to be significant should be included in a multivariable model - Need to define worsening renal failure over time. Did you look at any change in GFR, or a specific cut-off? Results: - Paragraph 2 is difficult to read. If the findings were non-significant, I think you can just say that all p-values were >0.05 and not include each p-value for each comparison - I am not sure what the linear regression adds to the manuscript, the p-values are really not significant if rounded to conventional two decimal places. I would not make much of these conclusions. To that effect, I don't think Figure 2 is informative. - Is there any clinical significance to having an NGAL greater than limit of detection? This should be explained. Authors could consider adding a column to their first table for those patients with baseline NGAL >118 and in the text just state that all comparisons were non-significant with p-values > 0.05, rather than list everything in the text. - In the section looking at renal parameters after one year, I don't think the outcome of "worsening eGFR" and "stable/improved eGFR" over 1 year was defined. Did they use any change, or a degree of change / category change? Why not perform a linear analysis for this? - Although technically telaprevir is a DAA, the term DAA has really come to represent second/third generation agents and not first generation PIs. I think the use of the term DAA is misleading. - In figure please include the N of patients - Did patients achieve SVR, or are they still on therapy? I think it would be more interesting to assess over longer term, after completion of therapy. It appears that at the time of this analysis, patients were still on therapy? - In the last paragraph and in figure 4 authors discuss two patients who developed an NGAL above the reference level. Does this have any clinical meaning? If they think this may have been related to telaprevir I think they should perform statistical comparisons between NGAL levels on patients not on teleprevir, however it doesn't seem as if they have an appropriate comparison group. I think numbers are two small to make any real conslusions. I don't think they should include figure 4. Discussion - I think the first sentence is misleading as only eight pat